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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,141	07/24/2003	Srinivas G. Rao	CYPR 101	5413

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EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/628,141	RAO ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,11-14 and 19* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,12-14 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1-2, 5-7, 11-14 & 19 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 8/2/2007 has been received and entered into the application. Accordingly, claims 1-2 and 5-7 have been amended and claims 3-4, 10, and 20-21 have been cancelled. Claim 11 remains withdrawn from consideration as being drawn to non-elected subject matter.

In view of the above amendments, the rejection of claims 1-3, 7, 10, and 12-13 under 35 U.S.C. 112, 1st Paragraph (Written Description) has been overcome and thus is *withdrawn*. Also, the amendments and Applicants' remarks have overcome the rejections not reiterated herein from the previous office action. Such rejections are hereby *withdrawn*. The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

Response to Arguments

Applicant's arguments filed 8/2/2007 have been fully considered but they fail to persuade the Examiner of an error in his determination that claims 1-7, 10, 12-14, and 19 (now 1-2, 5-7, 12-14, and 19) are *prima facie* obvious over Mouzin *et al.* and Moret *et al.* in view of Ruoff.

As Applicants correctly state, the Examiner has set forth an argument that Mouzin and Moret disclose that milnacipran is a dual norepinephrine serotonin reuptake inhibitor (NSRI) that may be used to treat depression (page 4 of Response). Further, Ruoff discloses that treatment in the patient with chronic pain is no different than in patients without pain. Accordingly, it is the Examiner's position that it would have been *prima facie* obvious that milnacipran would be an effective treatment for depression secondary to pain as instantly claimed (e.g., claim 1). In other

words, the skilled artisan would have been imbued with at least a reasonable expectation that milnacipran would be effective in treating depression that occurs in patients experiencing chronic pain.

Applicants traverse the present rejection and present several arguments in support of their assertion that it would not have been obvious to treat depression secondary to pain with milnacipran. Firstly, Applicants describe depression secondary to pain as a disorder characterized by co-morbidity of pain and *atypical* depression (emphasis in original). In contrast, Applicants submit, Mouzin, Moret, and Ruoff disclose the treatment of depression – not atypical depression. However, the fact that atypical depression is a "distinct subtype" of depression that "responds preferentially to monoamine oxidase inhibitors" (page 5 of Response) does not render any less obvious the claimed methods. The skilled artisan would have been imbued with at least a reasonable expectation that a drug effective in treating depression would predictably also be effective in treating different subtypes of depression. Secondly, Applicants argue that Ruoff "teaches away from using an NSRI" because Ruoff discloses that a single specie of NSRI (venlafaxine) is associated with serious side effects. However, as the Examiner has previously pointed out (see Office Action mailed 4/3/2007, page 8), milnacipran (an NSRI) has been used to treat depression for years with minimal side effects. As such, it is simply not the case that all NSRIs are associated with serious side effects. Finally, the fact that milnacipran is an effective treatment of major depression, in the doses instantly claimed (Moret et al., page 1218), would lead one skilled in the art to reasonably expect milnacipran would be an effective treatment of different subtypes of depression, including the instantly claimed depression secondary to pain.

Accordingly, the claims are deemed properly rejected as being obvious over Mouzin *et al.* and Moret *et al.* in view of Ruoff. The rejection of claims 1-2, 5-7, 12-14, and 19 is maintained for the reasons of record and reiterated below.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-2, 5-7, 12-14, and 19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mouzin *et al.* (U.S. Patent No. 4,478,836) in view of Moret *et al.* (1985) and Ruoff (1996).

Applicants' arguments filed 8/2/2007 have been fully considered but they are not persuasive. Applicants argue, *inter alia*, that Ruoff teaches away from the claimed methods because the reference discloses that the norepinephrine serotonin reuptake inhibitor (NSRI), venlafaxine, is associated with serious side effects. As such, applicants assert that one skilled in the art would not be motivated to administer a NSRI to treat depression secondary to pain (DSP).

Applicants further argue that Ruoff discloses that tricyclic antidepressants are considered second or third-line therapy when compared to the newer antidepressants. These arguments are not persuasive. Examiner respectively submits that the prior art: 1) teaches all of the claimed limitations; 2) provides ample motivation to combine Mouzin *et al.*, Moret *et al.* (1985) and Ruoff (1996); and 3) provides the skilled artisan with at least a reasonable expectation of success. The fact that venlafaxine is associated with side effects does not teach away from the claimed methods. This is only one example of an NSRI that happens to be associated with side effects. For example, the NSRI milnacipran has been used to treat depression for years with minimal side effects. Thus, one skilled in the art would recognize that NSRIs can safely be administered to treat depression. Mouzin *et al.* ('836 patent) disclose that milnacipran, salts of milnacipran, and derivatives thereof are useful in the treatment of depression (see especially Abstract). Moret *et al.* disclose that milnacipran is a dual norepinephrine (NE) serotonin (5-HT) reuptake inhibitor (see especially Abstract), has a NE:5-HT reuptake inhibition ratio of 2:1 (Table 4, page 1215), and can be used to treat depression at a dose of 50 mg twice a day (page 1218, last paragraph). Thus, Mouzin and Moret provide motivation to treat depression with the NSRI, milnacipran. Neither Mouzin *et al.* nor Moret *et al.* specifically teach the treatment of DSP with a NSRI. However, it is noted that DSP is a subtype of depression, characterized by the fact that it is generally observed in patients with chronic pain. One skilled in the art would have been imbued with at least a reasonable expectation that drugs suitable to treat depression would also be effective in treating DSP. This is especially true given the teachings of Ruoff.

Ruoff discloses that the neurotransmitters serotonin and norepinephrine have been implicated in both perception of pain and the pathogenesis of depression and that antidepressants

have been shown to be effective in the treatment of a variety of chronic pain syndromes, including peripheral neuropathic pain, headache, migraine, facial pain, fibrosis, and rheumatic pain (page S27). The reference further states that, "Regardless of whether depression is secondary to the pain syndrome or is the primary condition, the mood disorder should be thoroughly assessed and treated pharmacologically" (page S28, "Treatment Approaches"). Ruoff further discloses that the NSRI antidepressant, venlafaxine, exerts its antidepressant activity through selective inhibition of norepinephrine and serotonin uptake (Page S30, "Venlafaxine"). Thus, the reference provides further motivation to treat depression with an NSRI.

As noted by the Applicants, the relationship between chronic pain and depression is complex and not entirely understood. However, the treatment of depression secondary to pain is suggested by the reference to be the same as that for treatment of other types of depression. Ruoff states on Page S32, last paragraph that: "Clinicians must carefully assess patients prior to initiating antidepressant therapy. However, once depression is diagnosed, treatment in the patient with chronic pain is no different than in patients without pain. Antidepressant therapy should be started early and in full doses." Clearly, this statement, and in fact the entire disclosure of Ruoff, provides ample motivation to treat DSP with NSRIs. Ruoff explicitly states that the treatment of depression in patients with chronic pain (*i.e.* depression secondary to pain) is no different than treating other types of depression. As such, the skilled artisan would have been motivated to treat DSP with known antidepressants, including the NSRI taught by Mouzin and Moret.

Examiner respectfully maintains that the instantly claimed methods of treating DSP with NSRIs would have been *prima facie* obvious given the known use of the NSRI milnacipran to treat depression. In addition, the prior art is clear with regard to the relationship between pain

and depression; as Applicants have previously stated in their arguments, the relationship is complex and not entirely understood. However, it is the diagnosis of depression in patients having chronic pain that is complex. Once that diagnosis has been properly made, the treatment is, as suggested by Ruoff, no different than that used for depression without pain. In fact, at the time the invention was made, the prior art made no distinction in the treatment of depression and atypical depression secondary to pain.

Thus, claims 1-2, 5-7, 12-14, and 19 would have been *prima facie* obvious at the time the invention was made to one of ordinary skill in the art. This is especially true given that milnacipran was known in the art to be a dual norepinephrine serotonin uptake inhibitor useful in the treatment of depression due to its minimal side effects. The drug had been used, in the doses instantly claimed, to treat major depression (Moret *et al.*, page 1218). Lastly, Ruoff explicitly states that the treatment of depression in a patient having chronic pain is no different than in patients without pain. As such, the skilled artisan would be motivated to treat DSP with any antidepressant, including the NSRI milnacipran as taught by Mouzin *et al.* and Moret *et al.* and would have been imbued with at least a reasonable expectation that such treatment would be effective.

With respect to claim 10, it is generally obvious to combine two active agents, each of which is individually known to be useful in the treatment of the same condition. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said agents flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960). Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself. The natural presumption

that two individually known antidepressant agents would, when combined, provide a third composition also useful for treating depression flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption. Thus, the fact that milnacipran has been used to treat depression and sibutramine has the same mechanism of action, it follows that a combination of the two agents would also be effective in treating depression.

With respect to claims 14 and 19, the limitation wherein the DSP is "characterized by mood reactivity and neurovegetative symptoms present for more than two weeks" fails to distinguish the claimed methods from the prior art. It is not clear that this patient population is different from other patient populations having DSP. Further, as noted above, it would have been obvious to treat any form of depression with milnacipran given its use in the treatment of major depression.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

September 5, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER